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Report on the implementation of the EMA/CHMP think-tank recommendations

Areas addressed and recommendations on new emerging issues



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Abbreviations:

ATPs	Advanced Therapy Products
BM	Biomarker
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
CPWP	Working Party on Cell-Based Products
CP	Centralised procedure
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
ENCepp	European Network of Centres of Pharmacovigilance and Pharmacoepidemiology
EU	European Union
FDA	Food and Drug Administration
FU-SA	Follow-up scientific advice
GMP	Good Manufacturing Practise
GT	Gene therapy
GTWP	Gene Therapy Working Party
HCP	Health Care Professionals
HMA	Head of Medicines Agency
ICH	International Conference on Harmonisation
IMI	Innovative Medicines Initiative
IND	Investigational New Drug Application
ITF	Innovation Task Force
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MHLW/PMDA	Ministry of Health, Labour and Welfare (Japan)/ Pharmaceutical and Medial Devices Agency
M & S	Modelling and simulation
MoA	Mode of Action
NCA	National Competent Authority
OMP	Orphan Medicinal Product

PA	Protocol Assistance
PCWP	Patients' and Consumers' Working Party
PDCO	Paediatric Committee
PG	Pharmacogenomics
PGWP	Pharmacogenomics Working Party
PhVWP	Pharmacovigilance Working Party
PK	Pharmacokinetics
RA	Regulatory Authority
R&D	Research and Development
RMP	Risk Management Plan
SA	Scientific Advice
SAWP	Scientific Advice Working Party
SME	Small and Medium-sized Enterprise
SRA	Strategic Research Agenda
TC	Teleconference
WG	Working group
WP	Working Party

Introduction

Key objective of the European Medicines Agency (EMA, herein after “the Agency”) is to contribute making safe and efficacious medicines available to patients. Better medicines should reach the market timely and their evaluation made in line with the state-of-the-art scientific knowledge.

To achieve this objective the Agency keeps abreast with research and innovation in pharmaceuticals, acting on identified bottlenecks, on possibly redundant or irrelevant requirements and progressively modernising methods and procedures to support sound development and regulatory oversight of medicines.

A process improvement initiative launched by the Agency’s Executive Director in 2006 led to a number of actions to streamline and reinforce existing procedures: in this context, the “EMA/CHMP think-tank group on innovative drug development” was set up with the objective was to discuss with industry and academic stakeholders views on innovative drug development approaches, potential bottlenecks and areas where the regulators could provide support. A final report (hereafter named as “the TT report “) summarising the stakeholders’ views and incorporating recommendations from the think-tank group was finalised and adopted by the CHMP in March 2007 (EMA/127318/2007 dated 22 March 2007 (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004913.pdf); the relevant implementation plan was adopted in December 2007.

Projects addressing the recommendation of the think-tank have been incorporated in the CHMP and its working parties work programs 2008-2010 and other specific initiatives were supported by the Agency's Scientific Committees in the relevant areas of expertise. A number of recommendations have been also taken on board in the re-organisation of the Agency and will be further expanded in context with the changing environment.

Scope

This document reviews the think-tank group's recommendations implementation by the Agency in 2008-2010 to encourage and support innovative medicines development and availability in Europe.

Executive summary

As clearly indicated in the EMA's Road Map, the availability of scientific and technical resources within and in the European Medicines network system and their efficient operations are key factors for implementation and sustainability of initiatives at the European Medicines Agency level.

These two elements have been of key importance in the exercise of restructuring the Agency, and on these two main pillars therefore the Agency has based the TT recommendations’ implementation plan with the view of

- strengthening of the European networking model both at EU and global level
- reinforcing of the existing processes and
- establishing new procedures addressing globalisation of medicines development and approval

This report is released to the public with the view of providing an overview of actions taken and contributes to the background of further actions the Agency will undertake in line with the new Road Map to 2015.

1. Strengthening of the EU networking model

Actions under this heading aimed at both expanding the expertise available to the European medicines network system for scientific evaluation and guidelines as well as for improving operations efficiency.

1.1. *Expand experts' availability*

TT key recommendation was to expand experts' availability and involvement in scientific advice, in the scientific evaluation of regulatory submissions, such as MAA, OMP designation PIP decisions, preparation of guidelines, and ensure the best available scientific knowledge to the EU medicines network. Action has been taken notably by providing reliable estimates of resources required for forthcoming applications for main regulatory procedures such as OMP, PIP, MAA, MAA variations for extension of indications. The business pipeline project has been reinforced with dedicated resources; a more efficient portfolio interaction with the applicants, integrating the whole internal information with the general knowledge collated from public resources allows the early identification of focus areas of activities across the pharmaceutical industry as well as bottlenecks. The deliverables of the exercise support the internal budgeting and planning at the EMA level, ensure preparedness in the coordination of the activities, so that the Agency's can make decisions on priorities for the resources allocation and the committees' members can start considering the scientific resources needed among its members.

Extensive work has been put in place in conjunction with the Heads of Medicines Agencies to expand - according to the anticipated needs - the availability of experts to the main scientific committees, working parties and Scientific Advisory Groups, to best address the scientific key issues identified for each product undergoing regulatory evaluation.

The additional expertise has been made available as individual highly specialised experts, as working parties members and as Scientific Advisory Groups members.

Networks have been put in place to extend the possibility of address timely and efficiently transversal issues pertinent to defined areas such as pharmacovigilance and epidemiology (EnCEPP), paediatrics specialties (e.g. paediatric oncology) and patients' organisations.

In addition the Agency has developed a system of proactive consultation of learned society and of the scientific community as a whole on concept papers and guidelines. Written consultations and open face to face debates in workshops and conferences have been organised at the Agency to ensure the maximum interaction prior to the finalisation of documents setting out the expectations on scientific data useful for regulatory evaluation of medicines Benefit/Risk balance.

Participation of the Agency in to research networks in many different ways (e.g. IMI and DG-Research, FP6 and FP7 projects) has also contributed to the identification and interaction with additional experts.

Review of the transparency measures, of the conflict of interests policies and improvement of the resource-planning have been main priorities in the network and at the Agency level and have been critical to ensure adequate participation, independency and clarity of ultimately the decision making process within the EMA network.

1.2. Enabling infrastructures and IT tools to strengthen experts network communication

The agency in parallel implemented in 2008-2009 major actions on the building infrastructures and on the IT hardware, software and human resources, extending considerably the availability meeting rooms with of video- and teleconferencing facilities. The 1st and the 2nd floor of the Agency building have been entirely refurbished to provide for a full range of conference rooms equipped for remote conferencing. Existing conference rooms have been updated to allow substantial video and teleconferencing facilities and support teams established for the audiovisual as well as for the web-conferencing and broadcasting tools.

Contribution of specialised experts to core procedures using teleconferencing and other virtual facilities is now a routine in many scientific committees such as SAWP, COMP, CHMP, PDCO etc. This has also had a significant impact in extending the dialogue with the applicants at various stages of development. Up to August 2010, the Agency held more than 1543 VITERO conferencing accounts, with 60 new users a month, 1 to 5 Adobe-connect web-based conferences a week and 10-14 days a month broadcasting scientific committees' activities. The latter initiative also optimise the support provided by the secretariat now able to finalise the scientific documents following the committees discussions from the working positions within the offices and developments are ongoing to generate new tools for the EU assessors' network training.

Teleconferencing, videoconferencing and web-based meetings were used for several guideline-drafting groups but also for some plenary meetings of scientific committees and working parties. The availability of such facilities is contributing to improving the international interaction with other Agencies such as the FDA, PMDA, TGA, and Health Canada on the matter of common interest and on product-specific discussions.

The initiatives for the acceptance of e-submissions only documentation for regulatory review have been advancing with July 2009 marking the deadline for the acceptance of MAA on eCTD only. Electronic-only submission for applications for orphan designation and for Scientific Advice has proven to be a key element for the further progress of remote assessment work and interaction among assessors.

1.3. Integrated Scientific committees working parties operations

Operations of the CHMP working parties has been reviewed with the aim of better coordinate and integrate the activities of the various working parties with the scientific committees, avoiding redundancies and further rationalising the issuance of guidance documents. Drawing from the scientific expertise available new temporary working parties and drafting groups were established focussing their mandates and adapting the level of activity to the core business workload. A Working Parties Coordination Group chaired by the CHMP Chairman was established in July 2010, composed of chairpersons of the scientific committees, relevant secretariats and senior management, which in monthly virtual meetings review collegially the organisational aspects of the working parties and share status update of WPs and committees activities.

ITF briefing meetings, product-specific activities, international clusters activities, are included in the consideration of the Coordination Group. Guideline preparation is envisaged to take place via TC/WEB/Video links and other computer assisted methods reserving the face-to-face meetings for major discussions only, i.e. final transmission of documents to main committees.

1.4. Gain in efficiency and accrual of additional expertise

The above actions, altogether reducing the need for experts to travel to the Agency's premises lead to efficiency gains which in turn allow the extension of the experts' network with the establishment of Scientific Advisory Groups and ad hoc expert groups, as needed to ensure the best available expertise to the system. Since 2008 additional SAGs established cover the following therapeutic areas: cardiovascular diseases, viral diseases, neurology, psychiatry, diagnostics, and anti-infectives.

Ad hoc experts groups are also available to address particular areas of expertise working on an ad hoc basis such as the nanomedicines experts group and the 3R joint CHMP/CVMP expert group, addressing the Replacement, Reduction and Refinement of toxicology studies with alternative in vitro testing. With the aim of further extending the expertise available to the European Medicines network, and in line with the revised legislation, a number of additional initiatives took place to reinforce the interaction with civil society, clinical research networks and learned societies.

In the restructuring exercise of the Agency, a specific section within the medical information sector has been established to further support this important area and new processes have been put in place to ensure that the scientific community is engaged in the public scrutiny of our scientific deliverables in terms of products assessment, biomarkers qualification, guidelines etc. This is expected to contribute to opening new communication channels, expand the expertise available and stimulate interaction and collaboration.

Additional expertise has been made available to the system via the reinforced participation of Health Care Professional (HCP) and patients representatives to the life of the Agency. An increased number of patient and consumer representatives are being involved/part of EMA activities/newly established Committees (from 77 in 2007, to 165 in 2008, to 213 in 2009). Separately, a framework of interaction with healthcare professionals' organisations is being prepared in order to expand and formalise interaction in this area.

Another key development is the establishment of a dialogue with the European Network for Health Technology Assessment (EUnetHTA), representing the HTA bodies from across Europe. The collaboration is looking into how the information on the benefits and risks of medicines in European public assessment reports (EPARs) could make a better contribution to relative effectiveness assessments by HTA bodies. The Agency is also engaging in building capacity with HTA bodies for the provision of scientific advice early in medicine development and throughout the medicinal product's lifecycle With the aim of helping the applicants to provide the evidence that both groups need to determine a medicine's benefit-risk balance (reinforced scientific advice procedure, page 11).

1.5. Competence Development

Competence-development is another essential facet of the EU experts' network. Optimising resources also allows more time for competence development, notably by a series of training sessions, internal seminars and workshops where experts and assessors can build maintain and update scientific competence on a range of specialised topics.

Training sessions for the assessors are regularly held within certain Committee meetings, their working parties of the Agency, supported by a range of thematic conferences, workshops, and lectures. The Agency continues contributing to the work of the Joint Heads of Medicines Agencies/EMA Training Project Team, aimed at developing a strategy for training within the European medicines network and participate to the IMI training pillar projects to ensure that all efforts ongoing are pooled and could be used to sustain the scientific excellence of the European system.

The Agency also contributes to the IMI-funded project EMTRAIN (European Medicines Training focussing on tools and infrastructures), PHARMATRIN (focussing on curriculum development for specialists in medicinal products development and evaluation) and Eu2P, (focussing on an education programme for specialists and non-specialists in the fields of pharmacoepidemiology and pharmacovigilance).

The European Network of Paediatric Research at EMA (ENPREMA) has been established in 2010, and will be fully operational in 2011. This is a network of networks, to provide expertise and access to infrastructure for industry to conduct studies in children, define consistent and transparent quality standards, harmonise clinical trial procedures, and define strategies for resolving major challenges.

Modernisation of Training activities via TC and computer assisted methods started, extending the reach of training sessions and saving resources at the same time. For example, as part of efforts to identify alternative ways of addressing continuous education needs of the national competent authorities and the EMA, the Agency produced a DVD on influenza-pandemic preparedness training.

The Agency is also preparing for the future to extend the use of virtual tools such as “webinars” and remote access to broadcast records of major training events in order to further disseminating training opportunities.

1.6. Networking with EU Institutions and Agencies

The interactions with the European Commission Directorates have been efficiently maintained to a very high level throughout the period covered by this report. Regular monthly interaction with the DG of reference (DG Enterprise up to February 2010 and DG Santé and Consommateurs – SANCO, thereafter) has ensured that the scientific opinions prepared by the Agency prior to the decision-making process by the DG-ENT and SANCO was cleared on all matters with legal and regulatory policy implications. In addition regular reporting has been ensured by the Executive Director to the European Parliament and to the Council of Ministers, as appropriate (e.g. on pandemic flu vaccines).

The collaboration on matters of key importance for public health has been reinforced. The EU-wide response to the outbreak of the H1N1 influenza pandemic required a high level of cooperation and interaction between the European Commission and the EU agencies involved in the protection of public health.

The European Medicines Agency regularly briefed the Health Security Committee, a network of public health officials from the Member States coordinated by the European Commission. In addition, the Agency cooperated very closely during that period with the European Commission (DG SANCO and DG Enterprise) and ECDC in a trilateral task force. Work on vaccine surveillance resulted in a European strategy for influenza H1N1 vaccine benefit-risk monitoring.

On matters relevant to emerging science and technologies, such as genomics and nanotechnology, with direct impact on medicinal products development and standards the Agency has been working closely with specialised groups within the European Commission, DG Research, the European Pharmacopoeia and the European Drug Quality of Medicines networks (EDQM), the European Official Medicines Control Laboratories (OMCLS) and the European Food Safety Authority (EFSA).

2. New and reinforced procedures improving communication and interaction with regulators during the lifecycle of the products.

2.1. Drug development

A number of key processes were reviewed since 2007 and improvements were implemented. New procedures have been implemented in order to address new requirements set by the legislation coming in to effect in 2007-2010 as well as in preparation of changes in the pharmacovigilance area (see section Pharmacovigilance) .

In early development phase the Agency provides support and guidance via a number of services and activities associated with procedures which have been progressively reinforced or established as new to address growing needs of interaction and knowledge transfer prompted both by the application of emerging science and technologies (e.g. new statistical methods, -omics, nanotechnology, synthetic biology) available for drug development as well as new regulatory tools prompted by changes in legislation and update in requirements (e.g. regulation for paediatric medicines, Advanced Therapies Medicinal Products, Pharmacovigilance and Risk Management).

New procedures

With the Paediatric Regulation in force, the PDCO in the timeframe 2007-December 2010 has agreed more than 400 Paediatric Investigation Plans (PIPs), granted 176 product-specific waivers, and adopted several class waivers. Deferrals (to complete the paediatric development after the adult development) have been granted for 91% of new products, and for 64% of the authorised ones. The PDCO has received 207 applications pertaining to a variety of novel products including: recombinant DNA derived products, transgene-derived products, monoclonal antibodies, vaccines, cell-based products, nucleic acid-based products, oncolytic viruses, gene therapy, DNA vaccines, and antisense oligonucleotides.

Based on the implementation of new Regulation Advanced Therapy Medicinal Products (ATMPs) two new processes have been established in the Regulation and have been complemented with relevant technical and procedural guidelines:

- ATMPs classification: this procedure may allow at a very early stage, clarification on the positioning of the new ATMPs and the relevant technical requirements. The procedure is enriched by the long established experience of the Agency's Innovation Task Force which performs a technical review and contributes to the scientific consistency of the newly established procedure. Up to December 2010 39 of such classification have been performed and the final conclusions are published in the EMA web page (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000301.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800862c0&jsenabled=true)
- Certification of ATMPs developed by SMEs: this procedure is meant to provide an evaluation of the submitted quality and (when available) non-clinical studies performed by the applicant SME during their ATMPs development. Until December 2010 one certification has been finalised on the quality package of an ATMP.

In Scientific Advice a new procedure has been established for Qualification of novel development methods with an initial focus on Biomarkers and the introduction of an early appointment of the Biomarkers Qualification Team (BMQT). Guidance to applicants on the qualification of novel methodologies for drug development was adopted by the CHMP and published in January 2009. Now

the procedure is up and running there are two finalised and twelve ongoing. The process has been already streamlined and the guideline will be revised after ten completed qualification procedures.

Reinforced pre-authorisation procedures

Procedures have been reinforced throughout the Agency tasks with impact on:

- Innovation Task Force (ITF) forum
 - Briefing meetings systematically involving specialised experts and working parties
 - Peer Review of CHMP opinion on eligibility to EMA procedures and CAT Scientific recommendations on ATMPs classification
- OMPs designation
 - Common EMA/FDA application form
 - Exchange of information on case per case basis with FDA
 - Increased involvement of Agency resources (product classification, regulatory challenges)
- Scientific Advice
 - Pre-submission meetings with Coordinators
 - Peer review by CHMP
 - Discussion meetings during SA procedure
 - Involvement of additional specialised experts and working parties
 - Parallel Scientific Advice with FDA reinforced
 - Scientific Advice with involvement of WHO Experts has been reinforced
 - Scientific Advice with the participation of HTA bodies
 - Advice of development strategy
 - Advice on eligibility to conditional approval and accelerated review
 - Advice on Risk Management Plans reinforced

2.2. Marketing Authorisations via Centralised procedure

NEW procedures

- PUMA

The paediatric-use marketing authorisation (PUMA) is a new type of marketing authorisation. It may be requested for a medicine which is already authorised, but no longer covered by intellectual property rights (patent, supplementary protection certificate), and which will be exclusively developed for use in children. A first application was submitted in 2010 and it is expected to be completed in early 2011.

This type of marketing authorisation will cover the indication and appropriate formulation for the paediatric population. The development of this medicine in children will follow a paediatric investigation

plan (PIP). This PIP, which must discuss all paediatric subsets, will have to be agreed by the Paediatric Committee. A paediatric-use marketing authorisation will benefit from 10 years of market protection as a reward for the development in children.

- VARIATIONS OF MARKETING AUTHORISATION (Implementation of Commission Regulation (EC) No 1234/2008):
 - Concept of do-and-tell variations
 - Concept of work sharing introduced
 - Concept of variation grouping
 - Concept of quality design variations

All these new processes have been implemented has been introduced to optimise expert network workload and expertise.

Reinforced centralised procedure

- Rapporteurs' appointment: EMA has put steps in place to streamline the process for Rapporteurs' appointment to ensure the best available evaluation team for each product. The implementation steps for the EMA roadmap will elaborate on this further to support continuity of advice during the product life cycle and will be published in 2011.
- Involvement of additional specialised experts and working parties have been made available to the Committees as well as a Reinforced use of Scientific Advisory Groups Peer review is now standard process and has been reinforced with the addition of CHMP peer reviewers to the Rapporteur and co-Rapporteur evaluation teams.
- In the context of the implementation of the Advanced Therapy Medicinal Product (ATMP) Regulation, a new Committee has been put in place, The Committee on Advanced Therapy Medicinal Products, expanding the expertise available to the CHMP in the area. In addition a procedure to interact/collaborate with Medical Device Notified Bodies in the context of the evaluation of combined ATMPs with Medical devices, has been established increasing the potential network of expertise of the Agency in the field of medical devices in that context.
- In the review of the Orphan Medicinal Products designation status a number of additional transparency measures have been introduced including publication of the COMP reports and reinforcement of the evaluation of clinical benefit at the time of marketing authorisation with increased involvement of specialised experts and a streamlined procedure.

3. Global harmonisation

The need to further expand international cooperation in the context of the Agency's international strategy was included as an important part of the Agency's Road Map to 2015 and integrated in the consultation document, which was adopted by the Management Board for public consultation during its December 2010 meeting.

Recognising the increasing importance of international cooperation for safer and better medicines around the world, the EMA appointed an International Liaison Officer to oversee and develop further the Agency's cooperation with its international partners.

Confidentiality arrangements with third countries

Confidentiality arrangements with the medicines regulatory authorities of the US FDA (since 2003, extended 2005 and 2010), Japan (2007), Canada (2007), Australia (2009), Switzerland (2010) have been established and cover a number of areas of interactions. A series of exchanges of information on specific products and guidelines regularly take place within the framework of these confidentiality arrangements.

The efficiency of collaboration with the US FDA and the Japanese authorities was greatly increased when the notion of liaison placements was agreed. In June 2009, an FDA official took up a posting at the Agency, followed by an official from the Japanese authorities, who took up a liaison post in November 2009. The European Medicines Agency appointed a staff member as a liaison officer to the FDA in July 2009. These placements are currently still at a pilot phase.

The confidentiality arrangements with the US FDA are now firmly established. Interactions with the FDA doubled relative to the previous year. In October 2009 and in 2010, the two agencies reviewed their existing interaction, noted the increasing maturity and frequency of collaborative activities and agreed to add new clusters for further cooperation. A revised procedure for parallel scientific advice was also published and the number of such requests was seen to increase relative to previous years.

A joint good clinical practice (GCP) initiative with the FDA was launched on 1 September 2009, marking the start of an 18-month pilot. Additional efforts have been put in place in the area of Orphan Medicines and scientific advice (see section on reinforced procedures).

As regards paediatric medicines, the existing cluster with the FDA (monthly teleconferences, exchanges of staff, participation of FDA to expert meetings) has been implemented and recently enlarged to Canada and Japan as observers.

In the area of emerging science the Agency is currently chairing an informal forum on nano-pharmaceuticals to which US FDA, Health Canada, Australian TGA and Japan MHLW actively participate.

Increased activity took place within the veterinary medicines cluster of the cooperation agreement with the FDA, particularly in areas of technical requirements for authorisation and for the safety of veterinary products and their residues.

Outside the established confidentiality arrangements, the Agency participated in meetings with the Chinese State Food and Drug Administration, with particular focus on good manufacturing practice (GMP) and issues relating to clinical trials. A specific action plan on inspections is under development.

The Agency also supported the European Commission in discussions with India, within the framework of the working group on pharmaceuticals, and with Russia in the EU-Russian dialogue sub-group on pharmaceuticals.

Parallel EMA/FDA designation of orphan medicines

A process to simplify the administrative burden for designation of orphan medicines at the EMA and the United States Food and Drug Administration (FDA) was implemented in 2008. The two agencies agreed to recommend the use of a common application form for orphan designation. In 2008 thirty per cent of applications received used the common application form.

Cooperation with the US FDA progressed steadily. Initial agreement was reached on a new initiative, namely the submission of a common annual report on the progress of development for orphan-designated medicines to both agencies. Currently the agencies are discussing the harmonisation of the data necessary for the submission.

Paediatric medicines

The Agency, together with the Directorate-General Research of the European Commission, on the EU-side, and the National Institutes of Health (NIH) and the US FDA, on the side of the United States, started discussions on new priority lists for paediatric trials in the context of research into off-patent products. As part of these discussions, the Agency held a meeting with the NIH on criteria and methodology used for prioritisation. Twelve research projects have been financed by FP7, with over 56 million euro.

The Agency has also published in 2011 the results of the survey on the use of paediatric medicinal products in the EU.

Collaboration with the WHO

The EMA continued to collaborate with the WHO on medicinal products intended for markets outside the EU, quality matters, and international non-proprietary names (INN), and participated in the launch of the WHO initiative 'Make medicines child size' aimed at addressing the need for improved availability of safe medicines for children. The EMA is also actively part of the newly created Paediatric Medicines Regulatory Network coordinated by WHO.

In 2009, although interactions with the WHO were mainly focused on the H1N1 pandemic, discussions on streamlining Article 58 procedures, which allows the Agency to give scientific opinions on medicines that are intended for use outside the EU also took place. This may be used as a basis for future WHO prequalification procedure, with increase WHO insight participation and collaboration on article 58 medicinal product evaluations.

EMA staff fellowship to WHO was planned to start in 2011.

Clinical trials from third countries

In 2009, the EMA prepared a strategy paper on the acceptance of clinical trials conducted in third countries included in marketing authorisation applications through the centralised procedure (published in early 2009). The report 'Clinical trials submitted in marketing-authorisation applications to the EMA: Overview of patient recruitment and the geographical location of investigator sites' was published in October 2009. An International workshop on the ethical and good-clinical-practice aspects of clinical trials conducted in third countries was held in 2010 enabling participants to discuss and provide feedback on the 'Draft reflection paper on ethical and good-clinical-practice aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing authorisation applications to the European Medicines Agency', which was released for public consultation in May 2010.

In addition the Agency and the FDA launched a joint initiative to collaborate on international GCP inspection activities in July 2009.

The Agency, in close collaboration with the Member State Competent Authorities and its international partners, will invest in supporting capacity building and local awareness with the Regulatory Authorities, research communities and pharmaceutical industry of these countries.

ICH

Support was given to ICH initiatives on key technical guidelines* (Q8, Q9, Q 10, M3, S6 etc.) and innovative areas (Pharmacogenomics, Gene therapy). The Agency invested both in maintaining the existing topics and in providing further contributions to a series of activities with partners of the tripartite (EU-USA-Japan) International Conference on Harmonisation (ICH) and its veterinary equivalent (VICH).

Global Standardization

In 2009, the Agency took a key role in international standardisation efforts for the identification of medicinal products. The Agency continued to support and shape standards development with the International Organization for Standardization (ISO), European Committee for Standardization (CEN) and Health Level Seven (HL7). Outcomes are being integrated into ICT work programmes at the Agency.

4. Emerging science for clinical development and regulatory approval

New scientific knowledge of cell and molecular biology, enhanced by a number of enabling technologies such as genomics, proteomics, nanotechnology, has opened new therapeutic strategies yielding a number of multifunctional biologicals, hybrid biological/chemical entities, combined device/medicinal products and pushed forwards personalised medicines applications.

The EMA Innovation Task Force (ITF) role has been extended as the official landing zone for innovation, a discussion forum to open the door to emerging science, complementing and preparing the Agency and the Applicants for further interactions. Its remit and its scientific content reinforced with the systematic participation of specialised experts drawn from the network to the briefing meetings.

Since 2008, 77 briefing meetings were organised in the margins of main working parties for a total involving progressively an increasing number of scientists from working parties', academia, industry, EMA and FDA staff (347 experts involved in 2008 vs 525 in 2010). The ITF has in addition taken up a very active role in support to the Committee for Advanced Therapies contributing to review ATMPs classifications (and Tcon with CAT coordinator in case of controversial issues), and providing input in to the preparation of guidelines and reflection papers. The involvement of the ITF on emerging scientific areas included contributions on matters related to a variety of therapeutic areas encompassing gene and cell therapy, regenerative and personalised medicines, pharmacogenomics, nanotechnology applied to medicines, biomarkers, and novel statistical models. An ad hoc working group of experts on nanomedicines has been established, working also within the international nanomedicines forum involving regulatory authorities' representatives from US, Japan, Canada and Australia medicines agencies.

Reinforced interaction with IMI and FP7, contribution to international research consortia under the C-Path Initiative in the US, scientific collaboration with international centres of excellence (such as Duke's University and MIT) is an increasing feature of the activities of the Agency in support of Innovation in Pharmaceuticals. Among others of special mention is the IMI PROTECT project, coordinated by the EMA and aiming at enhancing the monitoring of the safety of medicinal products and to better evaluate and communicate their benefit-risk profile throughout their lifecycle. To this end, innovative tools and methodological standards will be developed.

Special attention has been devoted to formally support at EU level innovative medicines R&D methods including biomarkers, new imaging techniques, translational medicine, surrogate endpoints, modelling and simulation, statistical aspects. As mentioned under the scientific advice improvement area the Agency has established a new process aiming at the provision of scientific advice and opinions on the acceptability of novel methods. This new process has been formalised with the publication of the relevant guideline in 2008

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000122.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580022bb2).

Since the launch of this new scientific service, 14 qualification submissions have been undergoing such process which allows the scientific community a considerable degree of regulatory certainty in the use of such novel methods.

A wide range of actions implemented, including the organisation of Workshops as a tool to discuss with stakeholders new draft guidelines (e.g. guideline on First in man studies, or on cell based products) and emerging scientific approaches to drug development such as: biomarkers, adaptive designs, stem cell therapies, nanomedicines, neurodegenerative disorders and genetically determined Alzheimer and Huntington disease, Quality by design. The outcomes of those workshops are available in the EMA web page.

The increased dialogue with the Research based pharmaceutical industry and the academic groups has prompted the need to further work in integrating different competencies to address emerging medicines as new therapeutic approaches combining or integrating drugs, devices, diagnostics; in addition multifunctional nanotechnology systems and synthetic biology have been identified as the cutting edge area of novel science to be monitored.

Scientific preparedness via close contacts with the scientific community is key for the purpose of timely assessment of the applicability of current requirements, identification of neglected therapeutic areas for regulatory support and development of methods for early detection and management of associated risks to human and to environment during development as well as during use in clinical care of innovative medicines.

5. Pharmacovigilance

The Preparation for implementation of the new legislation has started in 2010 to prepare for the implementation of the new Pharmacovigilance legislation. A Cross-Agency Task Force has been set-up which reviewed all the arrangements to be put in place. Risk management system-guidelines were updated and scientific advice on risk management plans encouraged. Information on different scientific approaches in relation to risk minimisation activities in different Member States have been collected and analyzed, and principles for acceptable standards will be considered in upcoming revision of existing guidelines and in new ones to be developed.

As part of the outcome assessment for risk management plans, initiatives on the effectiveness of risk minimisation measures have been finalised.

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) together with the ENCePP Implementation Advisory Group (ENCIAG) were established in 2008. ENCIAG is an interim body, expected to champion the ENCePP project and support the EMA in the establishment and initial operation of the network including developing the database of ENCePP research centres, made publicly available in December 2009 and populated in 2010.

The access to Eudravigilance data/signal detection tools has been facilitated. Validation of the EudraVigilance Datawarehouse and Analysis System (EVDAS) continued during 2008, resulting in a more available, reliable and better performing EVDAS. The European Pharmacovigilance Issues Tracking Tool (EPITT) is now routinely used to support the signal-management process.

The main initiatives undertaken within the framework of the ERMS relate to the introduction as of the February 2008 CHMP meeting of an early notification system for communication within the EU Regulatory System Network as well as with the FDA on envisaged CHMP regulatory action due to safety related concerns.

This new procedure has allowed the EMA to take a more proactive and coherent approach towards communication on (emerging) safety issues. It has also helped to improve coordination of communication activities within the EU Regulatory System Network. Early Notification System for planned CHMP recommendations for regulatory action (based on identified safety concerns), introduced in 2008 to improve the coordination of communication to the general public in relation to safety concerns addressed by the Committee, was further developed in 2009 and 2010.

The Heads of Medicines Agencies also agreed on key principles on revised signal management in the EU. A pilot phase was launched in November 2008.

Work also progressed on the development of an EU Regulatory System Incident Management Plan. In November 2008, the Heads of Medicines Agencies agreed on key principles and on a procedure. A pilot phase for the EU Regulatory System Incident Management Plan for medicines for human use was launched on 1 June 2009. This plan is designed to improve the handling and coordination of any potential crisis with a medicine in the European medicines system. Since its launch, the management plan was triggered on several occasions.

Pharmacovigilance of antivirals and vaccines used during the influenza pandemic was a major activity in 2009. The Agency, in close collaboration with the European Centre for Disease Prevention and Control (ECDC) and the Heads of Medicines Agencies (HMA), developed a European strategy for benefit-risk monitoring of influenza A/H1N1 vaccines. The strategy was published in October 2009.

Substantial work has been put into post-pandemic lessons learnt meetings and documents, where pharmacovigilance issues have been represented.

RMP guideline is now being updated to include accumulated experience. Work is also ongoing on research projects looking at the outcome of risk-minimisation activities for centrally authorised medicines. A pilot phase on patients' representatives' participation in PhVWP meetings was successfully completed and work is underway to involve one patient representative as observer (and one alternate) in PhVWP meetings in 2010.

In April 2008, the Agency-led PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) project was accepted for funding by the Innovative Medicines Initiative Joint Undertaking (IMI JU). The official start date of the project was 1 September 2009.

In addition to PROTECT, the Agency also contributes to the IMI-funded project Eu2P, which focuses on the development of a comprehensive and flexible pan-European training and education programme for specialists and non-specialists in the fields of pharmacoepidemiology and pharmacovigilance.

6. Guidelines

New, quicker Question and Answer-documents from different working parties were piloted and in line with the current guideline on guidelines, more reflection papers than actual guidelines were produced (in particular for new emerging technologies and fast scientific developing areas).

(Therapeutic) area specific assessor networks were held together by corresponding area groups linked to relevant WPs. The CHMP, SAWP and other bodies were able to call upon specific expertise of these groups for products and guidelines and discussion in open conferences held with stakeholders at early stage of the preparation of key guidance documents.

Emphasis was placed on the new management tools related to the re-organisation of the Agency and of the Working parties, to harmonise the priorities for development of guidelines based on early consultation of experts and stakeholders.

In recent years, the Agency has also put in place a procedure to expand engagement with the scientific community during guideline preparation.

Scientific conference are organised to identify and discuss limitations and needs for guidelines with the scientific community prior to the actual finalisation of such regulatory documents. All draft guidelines are sent now for input to targeted European and International Learned Societies related to the guideline's area of interest. In 2009 42 draft guidelines were disseminated to a total of 1285 interested parties (31 on average). So far in 2010, 35 draft guidelines have been disseminated to a total of 804 interested parties (23 on average).

7. Antimicrobials

The Agency agreed to a request from the European Commission to work with EFSA, ECDC and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) to develop a joint report on the potential risk to man from the use of antimicrobials in animals.

In 2008 a Joint CHMP/PDCO WG with ECDC and Duke University was established and a joint report on multidrug-resistant bacteria in the EU and development of new antibacterial agents finalised.

A gap analysis on the current medical needs for antimicrobials and a priority list of pathogens was performed; and tailor-made requirements to encourage development of new medicines in this area considered.

Initiatives for incentives for developing old antimicrobials or niche products were discussed and proposals for further action made.

This included a presentation of the results of the GAP analysis and the results of an analysis made by the London School of Economics at a workshop during the Swedish presidency in September 2009. As a consequence, conclusions on innovative incentives for effective antibiotics were adopted by the EU Council. Among these conclusions is the need to identify appropriate regulatory instruments to facilitate early approval for new antibiotics for which a particular need exists. Moreover, a transatlantic taskforce on antimicrobial resistance has been established. The outcome of this work will be made available in 2011.

In 2010 a draft 'Guideline on the Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections' (CPMP/EWP/558/95 rev 2, 2010) was released for consultation and an international workshop planned to take place in February 2011 to create a forum for discussion among stakeholders – academics, regulators, industry – around the Agency guideline looking at issues related to the clinical

development of new antibacterial agents, including the design of studies in some of the major indications for use and studies targeting multidrug resistant bacteria.

Conclusions and recommendations

Three years after the adoption by the CHMP in December 2007 of an action plan for the implementation of think-tank group recommendations, this report describes the actions undertaken with the objective to support innovative drugs development for the benefit of patients.

Key actions initiated in response to the TT recommendations with respect to the direct support from the Agency to drug development included significant extension of the expertise available in the EU network, improved communication during the life-cycle of medicinal products (especially during early development) and the provision of balanced advice, dialogue and guidance in drug development and on new and emerging areas with closer international collaboration.

Significant effort has been put in reinforcing existing processes and in equipping new procedures defined by new legislation with appropriate expertise from the EU and the international experts' network. The policy on conflict of interests has been also revised to provide for more thorough and public available scrutiny of the EU experts' independence from the pharmaceuticals Industry.

Scientific advice on Risk Management Plans which was identified as key priority in 2007 has been successfully implemented and will be further developed in the coming years in line with the new legislation on Pharmacovigilance, which will further reinforce the role played by stakeholders in ensuring safety of pharmaceuticals in their lifecycle.

Important steps have been carried forwards to facilitate timely access to the market with the initiation of scientific Advice with HTAs and high level interaction with the HTA EU network (EUNeTA). In addition, the benefits associated with the usage of the new procedures of conditional approvals and accelerated review for faster access to the market may provide further room for early access to market.

Substantial engagement in global harmonisation and international interactions is ongoing following the orientations given by the think-tank and keeping the Agency in pace with the changes in priorities within the global pharmaceutical environment.

New legislation in the meantime has been adopted allowing for new initiatives and processes to be carried out in support of Paediatric medicines and Advanced Therapy medicinal products.

Involvement in scientific research projects of Public Private Partnerships, involving Regulators, Academia and in collaboration with industry is being implemented, is gradually growing and is part of the official work plans of the Agency.

Enhanced tools for transparency and communication have been put in place and the Agency has re-built a new corporate identity, new web site and reinforced the provision of information and documents to the public.

Many of the initiatives put in place as initial response to the TT recommendations are now being further reinforced and extended in order to satisfy needs which have emerged since.

The Road Map to 2015 indicates the priorities for the years to come (http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf).

Public statements and guidelines accompanying new legislation will contribute to maintain the European Regulatory system efficient and up to the challenges of changing global pharmaceutical, scientific and societal environment.